Dermal contact with furniture fabrics is a significant pathway of human exposure to brominated flame retardants

Abdallah, Mohamed; Harrad, Stuart

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Abstract

Despite extensive application in consumer products and concerns over their adverse health effects, how external exposure to brominated flame retardants (BFRs) contributes to their human body burdens is not yet fully understood. While recent studies focused on inadvertent indoor dust ingestion and diet as potential major pathways of exposure, dermal uptake has been largely overlooked. We provide the first experimentally-based assessment of dermal uptake of BFRs via contact with indoor dust and flame-retarded furniture fabrics. Results reveal substantial uptake from furniture fabrics (e.g. 8.1 ng pentaBDE/kg bw/day for adults in summer), exceeding the overall adult intake of pentaBDE estimated previously via other exposure pathways. For HBCDs, despite the low absorption fraction (<2.5%) from the studied fabrics, the estimated dermal uptake of UK adults and toddlers (101 and 76.9 ng/kg bw/day) exceed the reported average daily intakes of 7.9 and 43.0 ng/kg bw/day for these UK age groups. Conversely, uptake from dust was low (0.05 and 0.19 ng pentaBDE/kg bw/day for adults and toddlers, respectively), indicating previous pharmacokinetic approaches have overestimated significance of this route. Future exposure and risk assessment studies should consider dermal contact with treated products as a significant pathway of human exposure to BFRs and related chemicals.

Keywords	Dermal uptake; human exposure; BFRs; indoor dust; fabrics
Taxonomy	Human Environmental Health Exposure, Exposure Monitoring, Environmental Risk Assessment, Environmental Analysis

Corresponding Author	Mohamed Abdallah
Corresponding Author's Institution	University of Birmingham
Order of Authors	Mohamed Abdallah, Stuart Harrad
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Dr. Mohamed Abdallah
Division of Environmental Health & Risk Management,
School of Geography Earth and Environmental Sciences,
University of Birmingham,
Birmingham,
B15 2TT,
UK
Tel. +44 121 414 7297
Fax. +44 121 414 5527
E-mail: M.Abdallah@bham.ac.uk

The Editor,
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March 19, 2018

Submission of research article: "Dermal Contact with Furniture Fabrics Is a Significant Pathway of Human Exposure to Brominated Flame Retardants" By *Abdallah and Harrad*

Dear Sir/Madame,

I hereby submit the above work for consideration as a ***Research article*** in ***Environment International***. We believe that it warrants publication in this journal because it provides the first experimentally-based evidence of the significance of human dermal uptake of hazardous brominated chemicals via contact with flame-retarded consumer products. This is of broad relevance because exposure and risk assessment studies on these chemicals have hitherto completely overlooked this route of exposure, while focusing on other less significant pathways. Moreover, our results show that previous pharmacokinetic modelling approaches, have likely overestimated the contribution of dermal contact with indoor dust to human body burdens of brominated flame retardants. Therefore, this report is likely to shift the current focus of research in this area towards investigation of dermal contact with consumer products, rather than indoor dust and the inclusion of this significant pathway into current and future risk assessment models for these chemicals.
I confirm that none of the material in this has been published or is under consideration elsewhere, including the Internet.
My co-author share my mailing address and his email addresses is given below:
Professor Stuart Harrad (S.J.Harrad@bham.ac.uk)

I trust that I have submitted all the necessary information at the website, but if you require any further information, please don't hesitate to get in touch.

Best Regards,
Dr. Mohamed Abdallah

Research highlights

- First experimental assessment of human dermal uptake of BFRs from dust and furniture fabrics

- Dermal uptake from dust is likely overestimated by previous pharmacokinetic models

- Dermal uptake from flame-retarded fabrics is an important human exposure pathway

- Dermal contact with consumer products should be included in risk assessment models for BFRs

Abstract

Despite extensive application in consumer products and concerns over their adverse health effects, how external exposure to brominated flame retardants (BFRs) contributes to their human body burdens is not yet fully understood. While recent studies focused on inadvertent indoor dust ingestion and diet as potential major pathways of exposure, dermal uptake has been largely overlooked. We provide the first experimentally-based assessment of dermal uptake of BFRs via contact with indoor dust and flame-retarded furniture fabrics. Results reveal substantial uptake from furniture fabrics (e.g. 8.1 ng pentaBDE/kg bw/day for adults in summer), exceeding the overall adult intake of pentaBDE estimated previously via other exposure pathways. For HBCDs, despite the low absorption fraction (<2.5%) from the studied fabrics, the estimated dermal uptake of UK adults and toddlers (101 and 76.9 ng/kg bw/day) exceed the reported average daily intakes of 7.9 and 43.0 ng/kg bw/day for these UK age groups. Conversely, uptake from dust was low (0.05 and 0.19 ng pentaBDE/kg bw/day for adults and toddlers, respectively), indicating previous pharmacokinetic approaches may have overestimated the significance of this route. Future exposure and risk assessment studies should consider dermal contact with treated products as a significant pathway of human exposure to BFRs and related chemicals.

Dermal Contact with Furniture Fabrics Is a Significant Pathway of Human Exposure to Brominated Flame Retardants

Mohamed Abou-Elwafa Abdallah[1,2*], Stuart Harrad[1]

[1]Division of Environmental Health and Risk Management,
College of Life and Environmental Sciences,
University of Birmingham,
Birmingham, B15 2TT,
United Kingdom.

[2] Department of Analytical Chemistry,
Faculty of Pharmacy,
Assiut University,
71526 Assiut,
Egypt

*Correspondence to: M.abdallah@bham.ac.uk

Abstract

Despite extensive application in consumer products and concerns over their adverse health effects, how external exposure to brominated flame retardants (BFRs) contributes to their human body burdens is not yet fully understood. While recent studies focused on inadvertent indoor dust ingestion and diet as potential major pathways of exposure, dermal uptake has been largely overlooked. We provide the first experimentally-based assessment of dermal uptake of BFRs via contact with indoor dust and flame-retarded furniture fabrics. Results reveal substantial uptake from furniture fabrics (e.g. 8.1 ng pentaBDE/kg bw/day for adults in summer), exceeding the overall adult intake of pentaBDE estimated previously via other exposure pathways. For HBCDs, despite the low absorption fraction (<2.5%) from the studied fabrics, the estimated dermal uptake of UK adults and toddlers (101 and 76.9 ng/kg bw/day) exceed the reported average daily intakes of 7.9 and 43.0 ng/kg bw/day for these UK age groups. Conversely, uptake from dust was low (0.05 and 0.19 ng pentaBDE/kg bw/day for adults and toddlers, respectively), indicating previous pharmacokinetic approaches may have overestimated the significance of this route. Future exposure and risk assessment studies should consider dermal contact with treated products as a significant pathway of human exposure to BFRs and related chemicals.

Keywords: Dermal uptake; human exposure; BFRs; indoor dust; fabrics

Introduction

Brominated flame retardants (BFRs) are anthropogenic chemicals applied to a broad range of consumer products (e.g. foams, fabrics and plastics) to prevent or delay the onset of fire. As the majority are "*physically*" blended within rather than "*chemically*" bonded to polymeric materials, their emission from flame-retarded products to the environment is facile. The widely used BFRs (polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs)) have been detected in every studied environmental compartment and biological species (including humans) (Law et al., 2014; McGrath et al., 2017). This is of concern owing to their potential environmental and toxicological risks including: endocrine disruption, neurodevelopmental and behavioural disorders, hepatic abnormalities and cancer (Darnerud, 2008; Liu et al., 2017). Combined with their persistent and bioaccumulative characteristics, such evidence has triggered regulatory action to restrict the production and usage of PBDEs and HBCDs, culminating in their listing under the United Nations Environmental Programme (UNEP) Stockholm Convention on Persistent Organic Pollutants (POPs) (Stockholm convention on POPs, 2013). However, human exposure to PBDEs and HBCDs is likely to continue for some time, given the ubiquity of treated products remaining in use or entering the waste stream, coupled with their environmental persistence (Harrad and Diamond, 2006).

Current understanding is that human exposure to BFRs occurs mainly via a combination of diet, ingestion of indoor dust and inhalation of indoor air. However, it remains largely unknown how external exposure to these chemicals drives their human body burdens. This was demonstrated by the lack of significant associations between the concentrations of various BFRs in indoor air, dust or diet and their measured levels in human milk or serum (Roosens et al., 2009b; Toms et al., 2009; Watkins et al., 2012). Of

particular importance is the lack of explanation for the occasionally-reported high concentrations of BFRs in human milk or blood in several biomonitoring studies (Roosens et al., 2009a; Toms et al., 2009; Watkins et al., 2012). Understanding the cause of such high body burdens in such individuals is crucial to implement the necessary measures to reduce human exposure to these hazardous chemicals.

While a large volume of literature in the last decade focused on indoor dust ingestion as a pathway of human exposure to BFRs, recent studies have indicated the potential significance of the dermal pathway (Abbasi et al., 2016; Liu et al., 2017; Pawar et al., 2017). A Few studies have reported significant positive association between concentrations of BFRs measured in handwipes and those detected in human serum. However, this cannot be solely attributed to dermal exposure because ingestion via hand-to-mouth contact may be a major contributor to such associations (Hammel et al., 2017; Watkins et al., 2011). While previous pharmacokinetic (PK) modelling studies have suggested the potential significance of dermal exposure for PBDEs, these studies focused mainly on dermal uptake via contact with indoor dust and were subject to large uncertainties due to the lack of experimentally-relevant specific uptake rates for PBDEs (Lorber, 2008; Trudel et al., 2011). Blum et al. reported the dermal absorption of the flame retardant tris(2,3-dibromopropyl)phosphate (*tris-BP- banned in April 1977*) in ten children who were wearing or who had worn tris-BP-treated sleepwear (Blum et al., 1978). Imm et al. reported significant correlations ($P < 0.05$) between the lipid-adjusted serum concentrations of PBDEs in 44 adult participants and the total Br content in their sleeping pillows and vehicle seat cushions (Imm et al., 2009). The potential significance of dermal uptake of hazardous semi-volatile organic compounds (SVOCs) (e.g. Phthalates, PCBs, Chlorpyrifos and Nicotine) through contact with contaminated fabrics (e.g. clothing and bedding) was further highlighted by several authors (Beko et al.,

2018; Morrison et al., 2016; Weschler and Nazaroff, 2012). Furthermore, Saini et al. reported the sorption of airborne BFRs onto clothing fabrics suggesting potential implications for human dermal exposure via contact with contaminated clothing (Saini et al., 2016). More recently, Hammel et al. reported the presence of pentaBDE in sofa foam was associated with higher levels of BDE-47 in serum of 72 American adults ($P < 0.01$), which indicate that flame-retarded items (e.g. sofas) are likely important sources of exposure to these compounds via different pathways (Hammel et al., 2017). However, there is no experimental data on the extent of human dermal uptake of PBDEs from contact with indoor dust or flame-retarded fabrics and the significance of this route as a pathway of human exposure to PBDEs. Moreover, there is no available information on human dermal exposure to HBCDs via contact with indoor dust or flame-retarded products.

Against this background, the current study provides the first experimental investigation of dermal uptake via contact with indoor dust and/or flame-retarded fabrics as a potential major contributor to human body burdens of BFRs. To address this, we applied a standard *in vitro* protocol (Abdallah et al., 2015b) (Figure S1) to study human dermal uptake of tri- to hexa-BDEs (the major components of the pentaBDE commercial mixture) and HBCDs (α-, β- and γ- isomers) from indoor dust and flame-retarded fabrics, and thereby assess the significance of dermal uptake compared to other exposure pathways. Dermal uptake of BFRs from solid matrices (e.g. dust or fabrics) is a compound process involving multiple steps. Initially, the studied chemicals are released from the contact material to the physiological human skin surface film liquid (SSFL) (i.e. becomes *bioaccessible*). This is followed by penetration of the human skin barrier, formed mainly from the *stratum corneum*. Once the chemical passes through the corneous layer by passive diffusion, it follows the intracellular/intercellular routes of

penetration in the epidermis and dermis layers and subsequently reaches the blood stream (i.e. becomes *bioavailable*) (Pawar et al., 2017; Williams et al., 2005). To mimic real-life conditions, we used a simulated SSFL composed of sweat/sebum (1:1) mixture (Table S1) (Stefaniak and Harvey, 2008), real indoor dust and flame-retarded furniture fabric samples (Table S3), and viable *ex vivo* human skin kept under physiological conditions (37°C and 5% CO_2). In line with the reported high environmental concentrations and use of pentaBDE in North America and HBCD in Europe *(Law et al., 2014)*, the tested samples in this study included USA dust and fabric samples that contained elevated concentrations of pentaBDE congeners, along with dust and fabric samples from the UK that were HBCD-rich (Table S3). The aims of the current study are: (a) to provide the first experimental data on the dermal bioavailability of PBDEs and HBCDs via contact with indoor dust and furniture fabrics; (b) to investigate the potential factors influencing human dermal uptake of such BFRs; and (c) to estimate human dermal uptake of PBDEs and HBCDs via contact with dust and furniture fabric samples and evaluate the significance of this exposure pathway as a contributor to human body burdens of these contaminants.

Materials and Methods

Chemicals and Standards

All solvents and reagents used for preparation, extraction, clean-up and instrumental analysis of samples were of HPLC grade and obtained from Fisher Scientific (Loughborough, UK). Standard solutions (50 µg/mL, >99% purity) of BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, α-HBCD, β-HBCD and γ-HBCD were purchased from Wellington Laboratories (Guelph, ON, Canada). ^{13}C-labeled BDE-47, BDE-99, BDE-153, α-HBCD, β-HBCD and γ-HBCD used as internal (surrogate) standards, in addition to

^{13}C-BDE-100 and d_{18}-α-HBCD used as recovery determination (syringe) standards were purchased from the same company. Florisil® SPE cartridges were purchased from Supelco™ (Bellefonte, Pennsylvania, USA). All culture medium components (Table S1) and simulated human skin surface film liquid (SSFL) components (Table S2) were purchased from Sigma-Aldrich UK (Gillingham, Dorset, UK).

Test matrices

The penta-BDE commercial mixture (comprising mainly BDEs# 28, 47, 99, 100, 153 and 154) was predominantly used in North America. Therefore, concentrations of tri- to hexa- BDEs in indoor dust from North America are significantly higher than those reported in Europe (Harrad et al., 2008). In contrast, HBCDs have found greater use in Europe and Asia; hence their concentrations were higher in UK indoor dust compared to North America *(Law et al., 2014)*. Therefore, we used dust and fabric samples from the USA (NIST SRM 2585 dust and sofa fabric from California) to assess human dermal exposure to pentaBDE congeners and UK samples (house dust and armchair fabric from Birmingham) to study HBCD exposure. A full description of the dust and fabric samples applied in this study is provided in the Supporting Information.

Human skin

Freshly excised, healthy human upper thigh skin was obtained via Caltag Medsystems Ltd. (Buckingham, UK) from three consented female adults (aged 33, 35 and 36 years) following plastic surgery. Selection criteria included: Caucasian, no stretchmarks, no scars, no hair and full thickness skin without adipose tissue (870 ± 180 μm). Skin was kept on ice for no longer than 4 h prior to the onset of the *ex vivo* skin absorption studies. Upon receipt, *ex vivo* skin samples were equilibrated for 1 h with 3 mL of DMEM (Dulbecco's Modified Eagle's Medium) culture medium (Table S1) at 5 % CO_2 and 37 ˚C before use in dermal exposure experiments. The study protocol received the

required ethical approval (# ERN_12-1502) from the University of Birmingham's Medical, Engineering and Mathematics Ethical Review Committee.

Skin surface film liquid (SSFL)

Physiologically-simulated skin surface film liquid (SSFL) was prepared according to a previously reported method and US patent using over 25 different chemical components (Stefaniak and Harvey, 2006; Stefaniak and Harvey, 2008) including electrolytes, amino acids, triglycerides, vitamins and squalene (Table S2). The SSFL composition (1:1 sweat/sebum) and pH (5.3 ± 0.1) were adjusted to reflect relevant human physiological conditions (Stefaniak and Harvey, 2006).

Dermal exposure protocol

The dermal exposure experiments were performed using the static set-up approach (Figure S1). Skin tissues were mounted in standard Franz-type permeation devices with the stratum corneum facing up. The Franz cells had a joint internal diameter of 11.28 mm exposing an orifice area of 1 cm^2 with a receptor chamber size of 8 mL (PermeGear™, USA). To study the influence of skin hydration on dermal uptake of target BFRs, the skin surface was "moistened" with 100 $\mu L/cm^2$ and 50 $\mu L/cm^2$ of SSFL for the respective "wet contact" experiments; while no SSFL was added in the "dry contact" experiments. All experiments were performed in triplicate. Following 30 minutes equilibration, the tested matrices were applied onto the skin surface in the donor compartment. 50 mg of dust were applied onto 1 cm^2 of skin and shaken gently for 1 min to achieve a uniform spread of dust particles. For fabrics, 1 cm^2 of the tested fabric was placed on top of the skin surface with no further pressure on the fabric throughout the exposure time (24 h). For "neat" application a standard mixture of all the target compounds (5 ng/μL each, in acetone) was mixed and equilibrated with SSFL to achieve a final concentration of 0.5 ng/μL applied to the skin surface. A DMEM-based culture

medium (Table S1) was used as receptor fluid, maintained at 37 ± 1 °C and magnetically stirred. At fixed time points, aliquots of the receptor fluid (2 mL) were collected from the receptor compartment and immediately replaced with fresh fluid. After 24 hours, the entire receptor fluid was collected and the skin surface washed thoroughly with cotton buds impregnated in (1:1) hexane:ethyl acetate (5 times). The top five layers of the stratum corneum were removed via 5 consecutive stripping with adhesive tape. The skin tissues were removed from the permeation devices and both the donor and receptor compartments were washed separately (5 x 2 mL) with (1:1 v/v) hexane:ethyl acetate. All samples were stored at -20 ˚C until chemical analysis.

For simplicity, results of the dermal exposure protocol were grouped under three major categories for the mass balance (Table S10): (*i*) The "absorbed" category (cumulative mass of target BFRs in the receptor fluid over 24 h + receptor compartment wash), (*ii*) the "skin" category (mass of target BFRs in the skin tissue + tape strips after 24 h) and (*iii*) the "unabsorbed" category (mass of target BFRs in the skin surface wash after 24 h + donor compartment wash).

Sample extraction and Instrumental analysis

Each dermal exposure experiment generated five different types of samples comprising: receptor fluid, skin tissue, cotton buds and adhesive tape (used to thoroughly wipe the skin surface), donor and receptor compartment solvent washes. Samples were extracted according to a previously reported QuEChERs based method (Abdallah et al., 2015a; Abdallah et al., 2015b).

LC-MS/MS analysis of HBCDs and GC-MS analysis of PBDEs were performed according to previously reported methods (Abdallah et al., 2015a; Abdallah et al., 2015b). Further details are provided in the Supporting Information.

Quality assurance (QA)/Quality control (QC)

Several stages of QA/QC measurements were performed to check the performance of the permeation assay protocol. A "field" blank, comprising a skin tissue exposed to solvents only and treated as a sample, was performed with each sample batch (n= 9). None of the studied compounds were detected in the field blanks or solvent blanks (n=5, SSFL mixture and receptor fluid). Method LODs were estimated based on a 3:1 signal to noise ratio and ranged from 1-10 pg on the chromatographic column. Good recoveries of the ^{13}C-labeled internal standards (> 80 %) were obtained for all the studied BFRs indicating good efficiency of the extraction method (Table S7).

The integrity of the *ex vivo* skin applied was examined using the trans-epithelial electric resistance (TEER method). TEER measurements were performed using an EVOM^2 epithelial voltohmmeter equipped with STX2 electrodes and ENDOHM-12 specific TEER measurement chamber (World Precision Instruments, Hertfordshire, UK). An average resistance of 2360 ± 190 Ω was obtained for the skin patches used in this study. Patches with TEER < 2000 Ω were considered invalid and excluded from further testing.

In accordance with OECD guidelines, 5 % bovine serum albumin (BSA) was added to the receptor fluid to enhance the solubility of target analytes to ensure solubility is not the rate-limiting step in the dermal uptake process. To investigate the solubility of BFRs in the receptor fluid, we spiked 2 mL of the receptor fluid with a series of different concentrations of the target BFRs (in triplicate). The spiked receptor fluid was vortexed for 30 seconds and inspected visually for any phase separation or precipitation. If neither were observed, aliquots of the spiked receptor fluid were analyzed to assess the recovery of target compounds, compared to non-spiked samples. Good solubility and recovery (96.8 ± 3.4 %) of all target BFRs were observed up to a spiking level of 10 μg/mL (i.e. 20 μg in 2 mL of receptor fluid) for PBDEs and 15 μg/mL for HBCDs. This is higher than the observed concentrations of all target compounds in the performed

dermal exposure experiments, where the highest concentration was 1.39 ± 0.04 μg/mL of α-HBCD, less than 10 % of saturation solubility in the receptor fluid.

Both positive and negative controls were performed alongside each sample batch to further evaluate the performance and barrier function of the skin. Positive controls involved the exposure of the test tissue to Triton-X-100 which showed ~ 100 % permeation (n=5; 92 ± 7 %), while negative controls showed 0 % penetration of decabromodiphenyl ethane after 24 h exposure.

Assessment of Dermal uptake and dermal exposure parameters

Dermal uptake of the studied BFRs via dermal contact with indoor dust and furniture fabrics was estimated using the general equation:

$$\mathbf{DU} = \frac{\mathbf{C \times BSA \times AF \times IEF}}{\mathbf{BW \times 1000}} \quad (\mathbf{1})$$

Where DU = Daily dermal uptake (ng/kg bw/day), C = BFR concentration (ng/cm^2 for fabrics, ng/g for dust multiplied by the dust to skin adherence factor in g/cm^2), BSA = Body surface area exposed (cm^2), AF = Absorbed fraction (unitless), IEF = indoor exposure fraction (hours per day spent in contact with contaminated dust or fabric), BW = Body weight (kg).

The exposure parameters applied in equation 1 were obtained from the USEPA exposure factors handbook (USEPA, 2011) and are defined and summarized in Table S6. The following exposure scenarios were applied:

a) Summer: Assuming head, forearms, hands, thighs, lower legs and feet exposed to dust and the back of the forearms, half the back of the thighs, lower legs and the palms of the hands exposed to sofa fabric (i.e. wearing a typical short and half-sleeved shirt).

b) Winter: Assuming head, hands and feet exposed to dust and only the palms of the hands exposed to sofa fabric (i.e. wearing a typical full-length trousers and long-sleeve top).

Results and Discussion

Dermal bioavailability of BFRs

Our target PBDEs and HBCDs displayed wide variability in their ability to penetrate the skin under the applied experimental conditions (Table 1). BDE-28 (tri-brominated congener) displayed the highest average dermal penetration (4 % of original dose in dust), while BDE-154 (hexa-brominated) had the lowest penetration (0.5 % of original dose in fabric). α-HBCD was more effectively absorbed than its isomers β-HBCD and γ-HBCD from both dust and fabric. The dermally absorbed mass (detected in the receptor fluid) of all target BFRs following 24h-contact with tested fabrics were significantly higher (P<0.05) than those following contact with indoor dust (Table 1). Interestingly, when the absorbed mass was expressed as percent of the applied dose in the contact material, the percent of BFRs absorbed from tested fabrics were significantly lower (P<0.05) than from indoor dust (Table 1). This indicates the dermally absorbed fraction of BFRs varies with the type of contact matrix (i.e. dust or fabrics). In addition, the relative percent dermal absorption is a function of applied dose and doesn't necessarily result in higher internal exposure to the studied compound. Moreover, dermal absorption of BFRs was influenced by the degree of skin hydration during exposure with enhanced absorption from more "sweaty" skin (Figures S2 and S3). This may be partially attributed to the lipophilic sebum components in the SSFL (Table S2), which allow the release of BFRs from the studied solid matrices.

Collectively, our results highlight uncertainties associated with the current state of knowledge on dermal uptake of BFRs. While few studies exist on the dermal uptake of

phthalates (Gong et al., 2016; Gong et al., 2014) and other related chemicals (Moore et al., 2014), the available information on human dermal uptake of PBDEs stems from PK modelling approaches, where a single absorption factor was assumed (in the absence of experimental data) for all congeners regardless of their degree of bromination, molecular weight or physicochemical properties. Based on a single study of BDE-47 applied in acetone solution to *ex vivo* human skin, Trudel et al., used an average factor of 2 % for dermal uptake of all PBDE congeners from indoor dust (Trudel et al., 2011). The other PK study which estimated dermal uptake of PBDEs from contact with domestic dust assumed an absorbed fraction of 3 % for all congeners based on experimental studies on dioxins (Lorber, 2008). A more recent study(Liu et al., 2017) used concentrations of PBDEs in skin wipes and variable dermal absorption fractions for each congener (Abdallah et al., 2015a) to estimate dermal uptake of PBDEs via contact with indoor dust. While estimated uptakes were more realistic compared to PK studies, the authors highlighted several limitations including the assumption of 100 % mass transfer of all PBDEs in dust particles to the skin surface (Liu et al., 2017).

To our knowledge, there is no information on the dermal uptake of HBCDs via contact with indoor dust. Furthermore, exposure to flame retardants via dermal contact with consumer products has hitherto been completely overlooked despite the high concentrations of BFRs in these products compared to dust (Table S3).

Factors affecting human dermal uptake of BFRs

Our results show dermal uptake of PBDEs and HBCDs varies according to the physicochemical properties of each compound (Table S11). A significant (P<0.05) negative correlation exists between log K_{OW} of our target BFRs and their absorbed fractions from indoor dust (for fabrics, P=0.07). Interestingly, a positive correlation (P<0.05) was also observed between log K_{OW} and the percent of BFRs remaining within

skin tissue after 24 hours exposure (Figure 1). This is likely due to the time required for the more lipophilic, higher molecular weight BFRs to penetrate from the *stratum corneum* through the aqueous-based epidermis, which displays more resistance to the diffusion of highly lipophilic compounds (Durrheim et al., 1980). This is in agreement with the results of Frederiksen et al., who studied the dermal uptake of 10 "novel" flame retardants (NFRs) following neat application to *ex vivo* human skin (Frederiksen et al., 2016). The NFRs were absorbed into the skin, with most of each compound remaining in the epidermis and about an order of magnitude less in the dermis following 24h of exposure. Similar to our results, a significant negative linear relationship was observed between the skin permeability coefficient of the 10 NFRs and their log K_{OW} (Frederiksen et al., 2016). Nevertheless, percutaneous penetration is a dynamic process. Therefore, chemicals absorbed into the *stratum corneum* will continue to transfer into viable tissue layers. If there is no loss by metabolism, irreversible binding, or desquamation, then the mass of the chemical which entered the skin during the exposure period, will eventually become available to the body (USEPA, 1992).

Other factors influencing human dermal uptake of BFRs include the environmental matrix and the degree of skin hydration at the site of exposure.

Our results show significantly lower percent uptake of the studied BFRs from fabrics compared to indoor dust. In addition, the absorbed percentage values of BFRs from indoor dust were significantly lower than those from "neat" application of a standard mixture of the studied compounds in SSFL (Table S4). This is likely associated with the relative ease of contaminant transfer from the contacting solid matrix to the SSFL (*i.e. dermal bioaccessibility*) prior to subsequent diffusion through the *stratum corneum (Hoffman et al., 2017).* The relatively small particle size of indoor dust provides larger surface area for contact, which results in enhanced mass transfer of BFRs to the SSFL

(i.e. enhanced bioaccessibility) compared to furniture fabrics. Other factors that can largely influence the dermally absorbed fractions of BFRs include the initially applied dose and the fugacity of each studied compound (Kissel, 2011). Therefore, the use of a fixed absorption percent to assess the dermal uptake of a chemical (or group of chemicals), regardless of the contact matrix, exposure time, contaminant concentration and bioaccesibility is problematic and may lead to inaccurate results.

Moreover, a significant decrease in BFR absorbed fraction from both dust and fabrics was observed when the volume of SSFL was decreased (Table S5). This indicates that dermal uptake of BFRs from different matrices is influenced by the degree of skin hydration at the point of dermal contact. This may also be associated with the bioaccessibility of BFRs from solid matrices because a more hydrated (e.g. sweaty) skin may potentially enhance the transfer of BFRs to the SSFL (Fan et al., 2015; Sartorelli et al., 1999; Williams et al., 2004).

Assessment of human dermal uptake of BFRs from dust and fabrics

The results of our dermal *ex vivo* model were applied to derive realistic estimates of daily BFR uptake via dermal contact with indoor dust and contaminated furniture fabrics. In the absence of definitive data on daily dermal contact with indoor dust/fabrics, we used exposure parameters (Table S6) from the USEPA exposure factor handbook (USEPA, 2011). We considered a real-life exposure scenario based on typical apparel in summer and winter (Table 2) assuming adults contact with indoor dust for 6 hours/day and with sofa fabric for 4 hours/day. Toddlers (4 years) were assumed to have dermal contact with dust for 9 hours/day (because of their greater proximity to the floor and lower hygiene standards) and with sofa fabric for 2 hours/day (higher physical activity than adults). As expected, dermal uptake of PBDEs and HBCDs from dust and fabrics in summer was substantially higher than in winter due to the larger

surface area of exposed skin in summer (Table 2). More importantly, dermal exposures to PBDEs via contact with indoor dust ranged from (0.04 – 0.06 ng/kg bw/day) for adults and (0.14 – 0.24 ng/kg bw day) for children. These values are lower than pharmacokinetic-based estimates of median dermal uptake via contact with indoor dust by Lorber (0.83 ng/kg bw/day for American adults) (Lorber, 2008) and Johnston-Restrepo and Kannan (0.70 and 0.34 ng/kg bw/day for adults and toddlers, respectively) (Johnson-Restrepo and Kannan, 2009). Moreover, our estimates constitute (3.6 – 5.5 %) and (3.2 – 5.5 %) of the overall median daily intake of the studied PBDEs estimated by Trudel et al. for American adults and toddlers, respectively (Trudel et al., 2011). The estimated dermal uptake of □HBCDs via contact with indoor dust for adults (0.33 – 0.56 ng/kg bw/day) and toddlers (1.32 – 2.16 ng/kg bw/day) exceeds that for PBDEs (Table 2). While the absence of data on dermal uptake of HBCDs precludes comparison with previous studies, our estimates represent 5.1 – 8.7 % and 6.1 – 9.9 % of the estimated median overall □HBCDs intake of UK adults and toddlers, respectively (Abdallah and Harrad, 2011). Collectively, our results reveal that previous PK studies have likely overestimated human uptake of PBDEs via dermal contact with indoor dust, especially for adults, and likewise exaggerated the relative contribution of this pathway to the overall daily exposure to these hazardous chemicals.

Conversely, our "realistic" exposure scenario reveals adult dermal absorption of PBDEs from contact with a flame-retarded sofa fabric to be approximately two orders of magnitude higher than that via contact with indoor dust. The difference reduces to one order of magnitude when considering toddlers' dermal exposure (Table 2). This is due to the lower exposed body surface area of toddlers and the shorter time spent in contact with the sofa (2 h) compared to that with indoor dust (9 h). It's worth noting that our *in vitro* protocol involved no pressure on the fabric in contact with the exposed skin, while

sitting on furniture in real life applies a certain amount of pressure which may result in increased transdermal penetration of SVOCs (Cao et al., 2018; Morrison et al., 2017). Nevertheless, our conservative estimate for adult penta-BDE dermal uptake via contact with a flame-retarded sofa (8.1 ng/kg bw/day) during summer is higher than the average overall exposure (i.e. total for all pathways including diet, dust ingestion, inhalation and dermal contact with dust) of American adults estimated by Lorber (5.4 ng/kg bw/day) and Trudel et al (3.1 ng/kg bw/day). Moreover, the estimated adult uptake of BDE-99 from contact with the studied sofa (2.2 ng/kg bw/day) exceeds the No Adverse Effect Level (NOAEL) set by the Dutch National Institute for Public Health and the Environment (0.23 – 0.30 ng/kg bw/day using impaired spermatogenesis as the critical endpoint(Bakker et al., 2008)); while intake of BDE-47 (5.0 ng/kg bw/day) approaches the NOAEL of 7 ng/kg bw/day ((for which neurodevelopmental toxicity and thyroid toxicity were identified as the critical endpoints (Bokkers et al., 2011)). While the USEPA reference doses (RfD) of 100, 100 and 200 ng/kg bw/day for overall human exposure to BDEs 47, 99 and 153, respectively were not exceeded, our dermal absorption estimates (Table 2) still represent a considerable contribution to the overall daily intake of PBDEs.

The contribution of this pathway seems less prominent for toddlers, where our summer uptake estimate through contact with the sofa (6.1 ng/kg bw/day) is below the reported 34.5 ng/kg bw/day overall exposure of American 1-5 year toddlers (Lorber, 2008) and 10 ng/kg bw/day for the same age group by Trudel et al. (Trudel et al., 2011). The reported higher PBDE body burdens in toddlers than adults are likely associated with other exposure pathways such as increased hand-to-mouth behaviour and indoor dust ingestion (Trudel et al., 2011).

For HBCDs, despite the low absorption fraction from fabrics (Table 1), the estimated dermal uptake of UK adults and toddlers (101 and 76.9 ng/kg bw/day) exceed substantially the reported average daily intakes of 7.9 and 43.0 ng/kg bw/day for these UK age groups, respectively (Abdallah et al., 2008) (Figure 2).

Despite the lower absorbed fraction from fabrics (Table 1), the significance of BFR uptake via dermal contact with flame-retarded fabrics is evident compared to the other exposure pathways (Figure 2). While this exposure pathway has been hitherto completely overlooked, we believe it may offer a possible explanation for the occasional high BFR concentrations measured in human milk and/or plasma in various biomonitoring studies. For example, the median concentration of PBDEs in 31 American adult serum samples was 27.7 ng/g lipid weight, while the maximum concentration was 348 ng/g lipid weight (Watkins et al., 2012). Similarly, the median □HBCD concentration in 34 UK human milk samples was 3.8 ng/g lipid weight, while the maximum concentration was 22.4 ng/g lipid weight (Abdallah and Harrad, 2011). Such elevated concentrations could not be explained by pharmacokinetic models even at worst-case scenario assumptions (Abdallah and Harrad, 2011; Trudel et al., 2011).

This study provides the first experimental evidence that dermal contact with flame-retarded consumer products contributes substantially to human body burdens of PBDEs and HBCDs. Future risk assessments for these contaminants as well as emerging BFRs and phosphorous flame retardants marketed as replacements for PBDEs and HBCD should consider dermal contact with treated products as a potential significant human exposure pathway to these hazardous chemicals.

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Supplementary Material

Full description of dust and fabric samples, analytical methodology, dermal absorption parameters and human exposure assessment are provided as supplementary material.

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Tables

Table 1: Absorbed fraction of target BFRs following 24 h exposure of *ex vivo* human skin to indoor dust and sofa fabrics*.

	% of applied dose		Absorbed mass (ng)	
	Dust	**Fabric**	**Dust**	**Fabric**
BDE-28	4.0 ± 0.5	3.8 ± 0.7	0.10 ± 0.01	25 ± 4.9
BDE-47	2.3 ± 0.3	2.0 ± 0.1	0.60 ± 0.03	770 ± 26
BDE-99	1.4 ± 0.1	1.2 ± 0.1	0.64 ± 0.04	343 ± 23
BDE-100	1.4 ± 0.2	1.3 ± 0.2	0.11 ± 0.02	87 ± 13
BDE-153	0.7 ± 0.1	0.5 ± 0.2	0.04 ± 0.01	13 ± 3.9
BDE-154	0.7 ± 0.1	0.5 ± 0.1	0.03 ± 0.01	11 ± 3.4
α-HBCD	5.6 ± 1.1	2.3 ± 0.1	7.1 ± 1.4	12745 ± 559
β-HBCD	3.9 ± 1.5	1.7 ± 0.1	1.8 ± 0.7	2509 ± 129
γ-HBCD	2.8 ± 0.8	1.4 ± 0.2	5.0 ± 1.3	432 ± 78

* Results presented as average ± standard deviation (n=3), skin surface was wetted with 100 µL of SSFL prior to matrix application.

Table 2: Estimated human daily exposure (ng/kg bw/day) to PBDEs and HBCDs via dermal contact with indoor dust and sofa fabrics.

	Male adult[$]				Female adult				Toddler[#] (male/female 4 years)			
Scenario	Summer*		Winter**		Summer		Winter		Summer		Winter	
BFR	Dust	Fabric	Dust	Fabric	Dust	Fabric	Dust	Fabric	Dust	Fabric	Dust	Fabric
BDE-28	0.00	0.17	0.00	0.03	0.00	0.14	0.00	0.03	0.01	0.12	0.01	0.03
BDE-47	0.02	5.45	0.02	0.98	0.02	4.48	0.01	0.80	0.09	3.78	0.08	0.79
BDE-99	0.03	2.42	0.02	0.44	0.02	2.00	0.02	0.36	0.10	1.68	0.06	0.35
BDE-100	0.00	0.62	0.00	0.11	0.00	0.51	0.00	0.09	0.02	0.43	0.01	0.09
BDE-153	0.00	0.09	0.00	0.02	0.00	0.08	0.00	0.01	0.01	0.07	0.00	0.01
BDE-154	0.00	0.08	0.00	0.01	0.00	0.06	0.00	0.01	0.00	0.05	0.00	0.01
□penta-BDEs	**0.06**	**8.83**	**0.04**	**1.59**	**0.05**	**7.27**	**0.04**	**1.29**	**0.23**	**6.13**	**0.16**	**1.28**
α-HBCD	0.30	90.15	0.20	16.23	0.25	74.19	0.17	13.20	1.11	62.50	0.69	12.99
β-HBCD	0.07	17.75	0.05	3.20	0.06	14.61	0.04	2.60	0.27	12.30	0.17	2.57
γ-HBCD	0.21	3.06	0.14	0.55	0.17	2.51	0.12	0.45	0.78	2.12	0.48	0.45
□HBCDs	**0.58**	**110.95**	**0.39**	**19.98**	**0.48**	**91.31**	**0.33**	**16.25**	**2.16**	**76.92**	**1.34**	**16.01**

* Assuming head, forearms, hands, thighs, lower legs and feet exposed to dust and the back of the forearms, half the back of the thighs, lower legs and the palms of the hands exposed to sofa fabric (i.e. wearing a typical pair of shorts and short-sleeved shirt).

** Assuming head, hands and feet exposed to dust and only the palms of the hands exposed to sofa fabric (i.e. wearing typical full-length trousers and long-sleeve top).

[$] Assuming adult bodyweight of 70 kg, adults exposed to dust for 6h/day and sit on sofa/chair for 4h/day.

[#] Assuming toddler bodyweight of 15 kg, toddlers exposed to dust for 9h/day and sit on sofa/chair for 2h/day.

Figures

Figure 1: Scatter plots of Log K_{OW} of target BFRs against the percent of dose absorbed and remaining within the human skin tissue following 24 h exposure to indoor dust (a) and sofa fabrics (b).

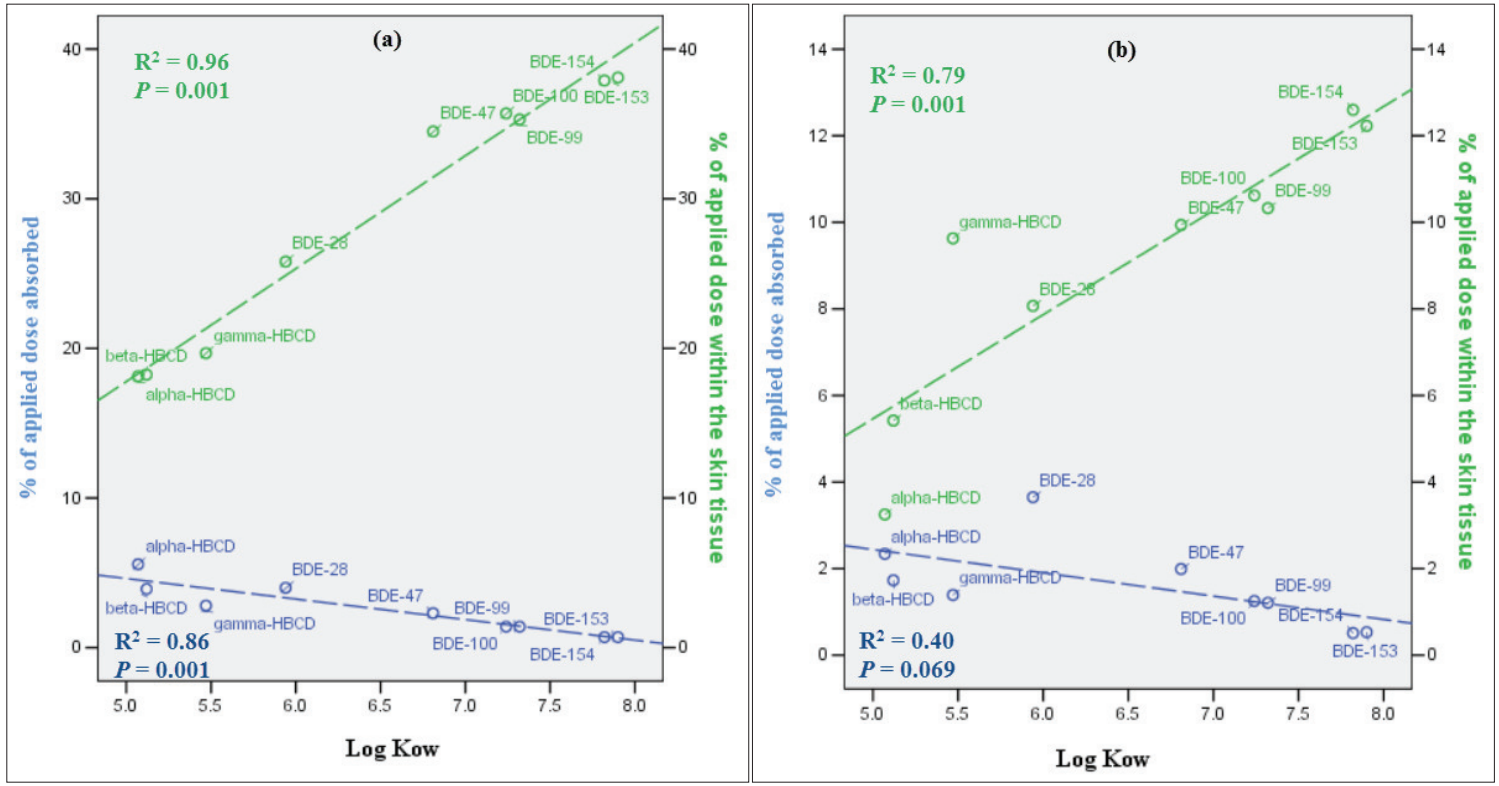
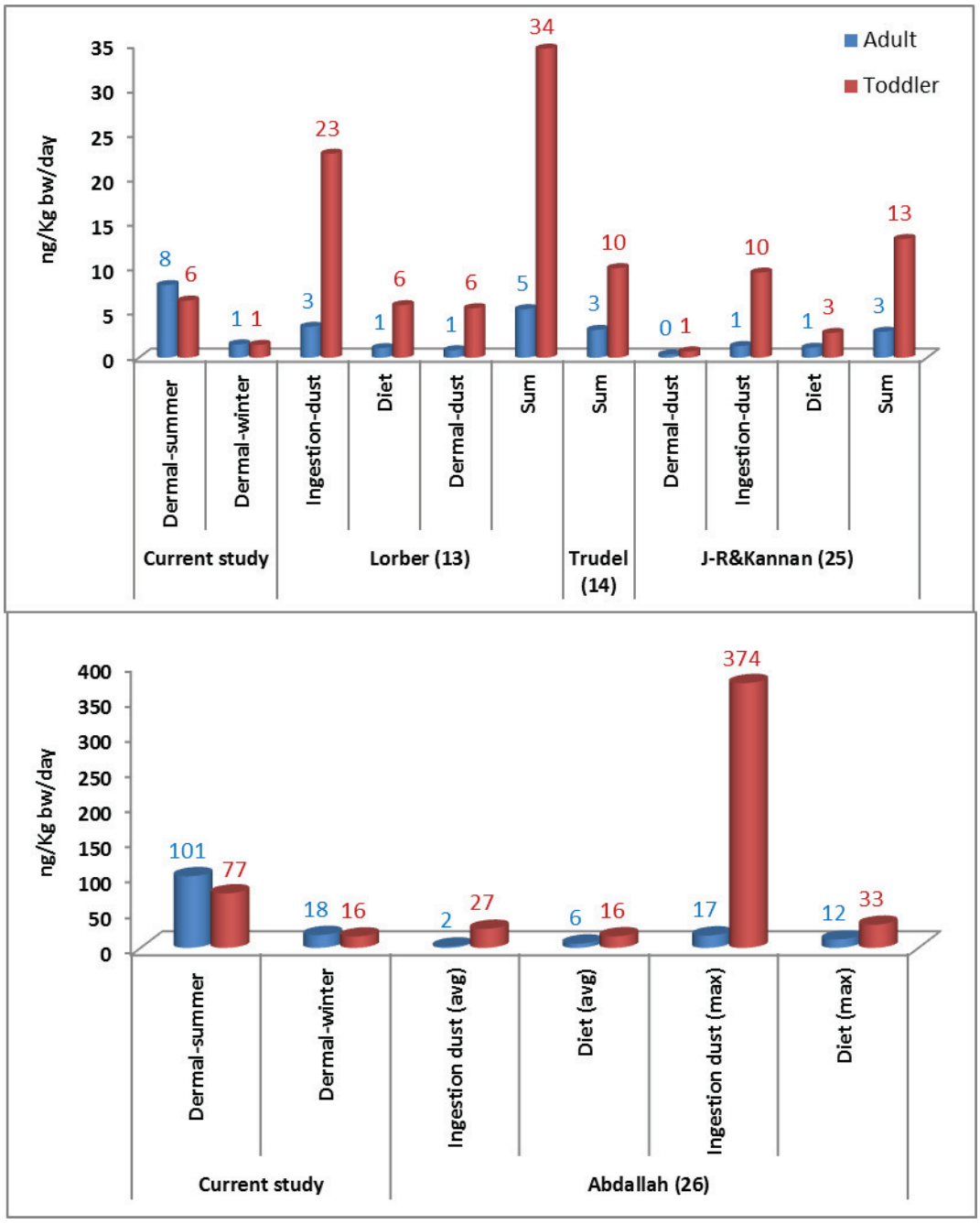


Figure 2: Estimated human dermal uptake (ng/kg bw/day) of (top) PBDEs and (bottom) HBCDs via dermal contact with furniture fabrics compared to reported median intakes via other major exposure pathways.



Supplementary Material for

Dermal Contact with Furniture Fabrics Is a Significant Pathway of Human Exposure to Brominated Flame Retardants

Mohamed Abou-Elwafa Abdallah[1,2*], Stuart Harrad[1]

[1]Division of Environmental Health and Risk Management,
College of Life and Environmental Sciences,
University of Birmingham,
Birmingham, B15 2TT,
United Kingdom.

[2] Department of Analytical Chemistry,
Faculty of Pharmacy,
Assiut University,
71526 Assiut,
Egypt

21 Pages, 10 table, 5 figures and method description.

* Corresponding author
E-mail: M.abdallah@bham.ac.uk

Sample description

NIST SRM 2585 indoor dust

Homogenous indoor dust collected from homes, cleaning services, motels, and hotels in the states of North Carolina, Maryland, Ohio, New Jersey, Montana, and Wisconsin during 1993 and 1994. This dust has a particle size < 100 μm and moisture content of 2.1 ± 0.1 %. Concentrations of target PBDEs in SRM2585 are provided in Table S3.

MD3 indoor dust

Homogenous indoor dust sample collected from a house in Birmingham, UK in 2008. This dust has a particle size < 100 μm and moisture content of 2.3 ± 0.1 %. Measured concentrations of HBCDs in MD3 are provided in Table S3.

Sofa fabrics

Sample US-H4 was obtained from a sofa bought in the late 1990s in California, USA. Sample UK-H5 was obtained from a couch bought in 1999 and used in a house in Birmingham, UK. Measured concentrations of penta-BDE congeners and HBCDs in US-H4 and UK-H5 are provided in Table S3.

Sample extraction

Each dermal exposure experiment generated five different types of samples comprising: receptor fluid, skin tissue, cotton buds and adhesive tape (used to thoroughly wipe the skin surface), donor and receptor compartment solvent washes.

The receptor fluid, skin tissue and cotton buds samples were extracted according to a previously reported QuEChERs based method.[1, 2] Briefly, each sample was spiked with 30 ng ^{13}C-α-, β-, γ-HBCDs, BDE-77, BDE-128 and ^{13}C-BDE-209 used as internal (surrogate) standards. Extraction was performed using 2 ml of (1:1) hexane:ethyl acetate mixture and vortexing for 2 minutes, followed by ultrasonication for 5 minutes and centrifugation at 4,000 *g* for 3 minutes. This extraction cycle was repeated twice before the combined organic extracts were evaporated under a gentle stream of N_2. The final extract was reconstituted into 100 μl of methanol containing 100 pg/ μl of d_{18}- α-HBCD used as recovery (syringe) standard for HBCD analysis or 100 μl of isooctane containing 100 pg/μl of PCB-129 used as recovery (syringe) standard for PBDE analysis.

The donor and receptor compartment washes were spiked with 30 ng of the ^{13}C-labeled internal standard mixture prior to direct evaporation under a gentle stream of N_2. Target analytes were reconstituted in 100 μL of methanol containing 100 pg/ μl of d_{18}- α-HBCD for HBCD analysis or 100 μl of isooctane containing 100 pg/μl of PCB-129 for PBDE analysis.

Instrumental analysis

LC-MS/MS analysis of HBCDs was performed according to a previously reported method.[1] Chromatographic separation of α-, β- and γ-HBCDs was achieved using a dual pump Shimadzu LC-20AB Prominence liquid chromatograph (Kyoto, Japan) equipped with SIL-20A autosampler, a DGU-20A3 vacuum degasser and a Varian Pursuit XRS3 C_{18} analytical column (150 mm × 2 mm I.D., 3 μm particle size). A mobile phase of (a) 1:1 methanol/water with 2 mM ammonium acetate and (b) methanol at a flow rate of 120 μL min^{-1} was applied for elution of the target compounds; starting at 50 % (b) then increased linearly to 100 % (b) over 3 min, held for 5 min, followed by a linear decrease to 65 % (b) over 2.5 min and held for 5.5 min. TBBP-A was eluted as a single peak at 9 min. The three main HBCD diastereomers were baseline separated on the C_{18} column with retention times of 12.3, 12.9 and 13.3 min for α-, β- and γ- HBCD, respectively. Mass spectrometric analysis was

performed using a Sciex API 2000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA, USA) operated in electrospray negative ionization (ESI) mode. MS/MS detection operated in the multiple reaction monitoring (MRM) mode was used for quantitative determination of HBCD isomers based on *m/z* 640.6→79, *m/z* 652.4→79 and *m/z* 657.7→ 79 for the native, ^{13}C-labelled and d_{18}-labelled diastereomers, respectively.
GC-MS analysis of PBDEs was performed using a TRACE 1310™ GC coupled to a ISQ™ Single Quadrupole mass spectrometer (Thermo Fisher Scientific, Austin, TX, USA) operated in negative chemical ionisation (NCI) according to the previously described method.[2] Separation of target PBDEs was performed on Agilent DB-5 capillary column (15m x 0.25mm; 0.1 µm). The mass spectrometer was run in selected ion monitoring (SIM) with ion source, quadrupole and mass transfer line temperatures set at 230, 150 and300 °C, respectively. Helium was used as carrier gas at constant flow (1.0 ml/min) with methane as moderating (or reagent) gas. One µL of the extract was injected in solvent vent mode (injector temperature at 90 °C for 0.06 min, then increased at 700 °C/min to 305 °C, vent time 0.04 min, vent flow 50 ml/min). The splitless time was 1.5 min. The GC temperature program started at 90 °C for 1.5 min, then ramped linearly at 15 °C/min to 295 °C, which was kept for 15 min. Dwell times were 30 ms. Ions m/z 79 and 81, together with ions m/z 484.7/486.7 and 494.7/496.7 for BDE 209 and ^{13}C12-BDE 209, respectively, were monitored for the entire run.

Assessment of dermal absorption parameters for the studied BFRs[3]

A quantitative description of test compound permeation through the skin barrier can be derived from Fick's first law of diffusion as follows:

$$J_{ss} = \frac{\Delta m}{\Delta t . A} = \frac{D . K . \Delta C}{\Delta x} \qquad (2)$$

Where J_{ss} = steady-state flux [ng/cm^2.h]; Δm = permeated mass [ng]; Δt = time interval [h]; D = diffusion coefficient [cm^2/h]; K = partition coefficient; A = area [cm^2]; Δc = concentration difference across the membrane [ng/cm^3]; Δx: thickness of membrane [cm].
When using infinite-dose configurations, i.e. in which the donor concentration far exceeds the concentration in the receptor compartment ($C_D >> C_A$), ΔC can be replaced by the known donor concentration, C_D, and the permeated mass per time assumed constant. Therefore, the apparent permeation coefficient (***Kp, cm/h***), which represents an independent measure of the membrane resistance against permeation of the examined substance, can be calculated as:

$$Kp = \frac{J_{ss}}{C_D} \qquad (3)$$

For each permeation experiment, cumulative amounts of the permeated compounds in the receptor fluid per unit area of exposed skin (ng/cm^2) were plotted versus time (hours). Steady state conditions were indicated by a linear regression line ($R^2 \geq 0.9$, $P < 0.05$, Table S8), the slope of which represents the flux (J_{ss}). Determination of the start and upper boundary of the linear range (i.e. steady state conditions) was achieved according to the method previously described by Niedorf et al.[3]
Following the contact of target BFRs with the skin, each compound needs to partition into the *stratum corneum* and diffuse through the epidermal cells before reaching the receptor fluid. This results in a lag time, t_{lag}, with non-detectable flux. The t_{lag} is represented by the time intercept (i.e. x-axis intercept) of the regression line over the linear region of the permeation curve (Figures S4). Hence, t_{lag} can be calculated from equation 3:

$$t_{lag} = \frac{b_0}{J_{ss}} \ldots\ldots\ldots\ldots (4)$$

Where b_0 refers to the y-axis intercept of the linear regression line and J_{ss} is the slope.

Results are presented as the arithmetic mean of 3 replicates ± standard deviation (SD). Statistical analysis was performed using SPSS 21.0 software package. Differences in skin permeation were evaluated by the paired student t-test between 2 datasets. A Games-Howell test was used for analysis of variance (ANOVA) among several datasets; $p < 0.05$ was regarded to indicate a statistically significant difference.

Fig. S1a.
A schematic representation of the dermal exposure configuration applied in this study.

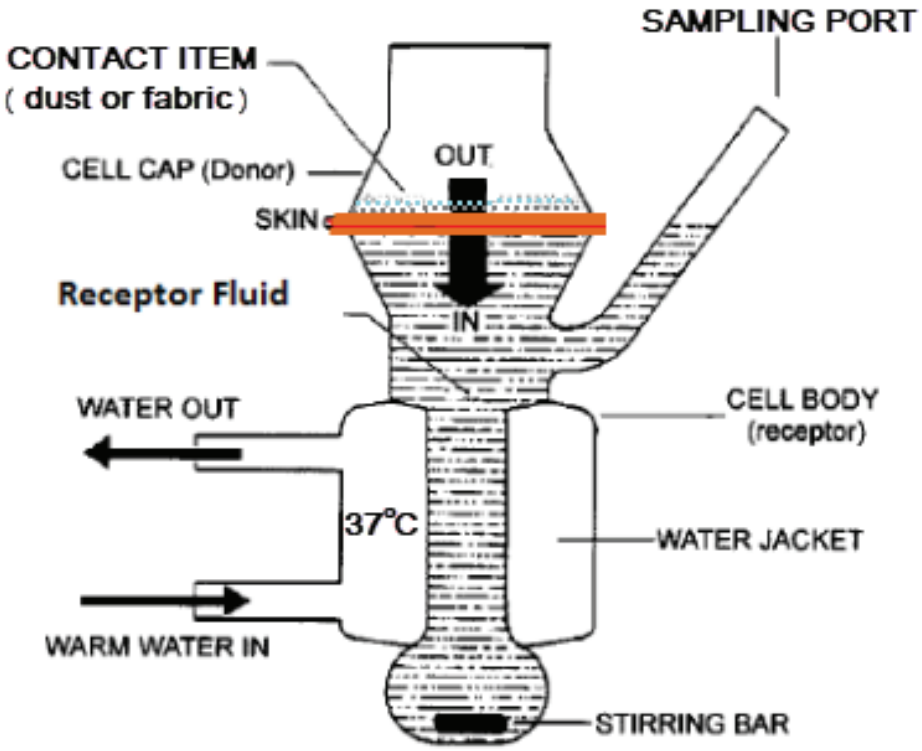
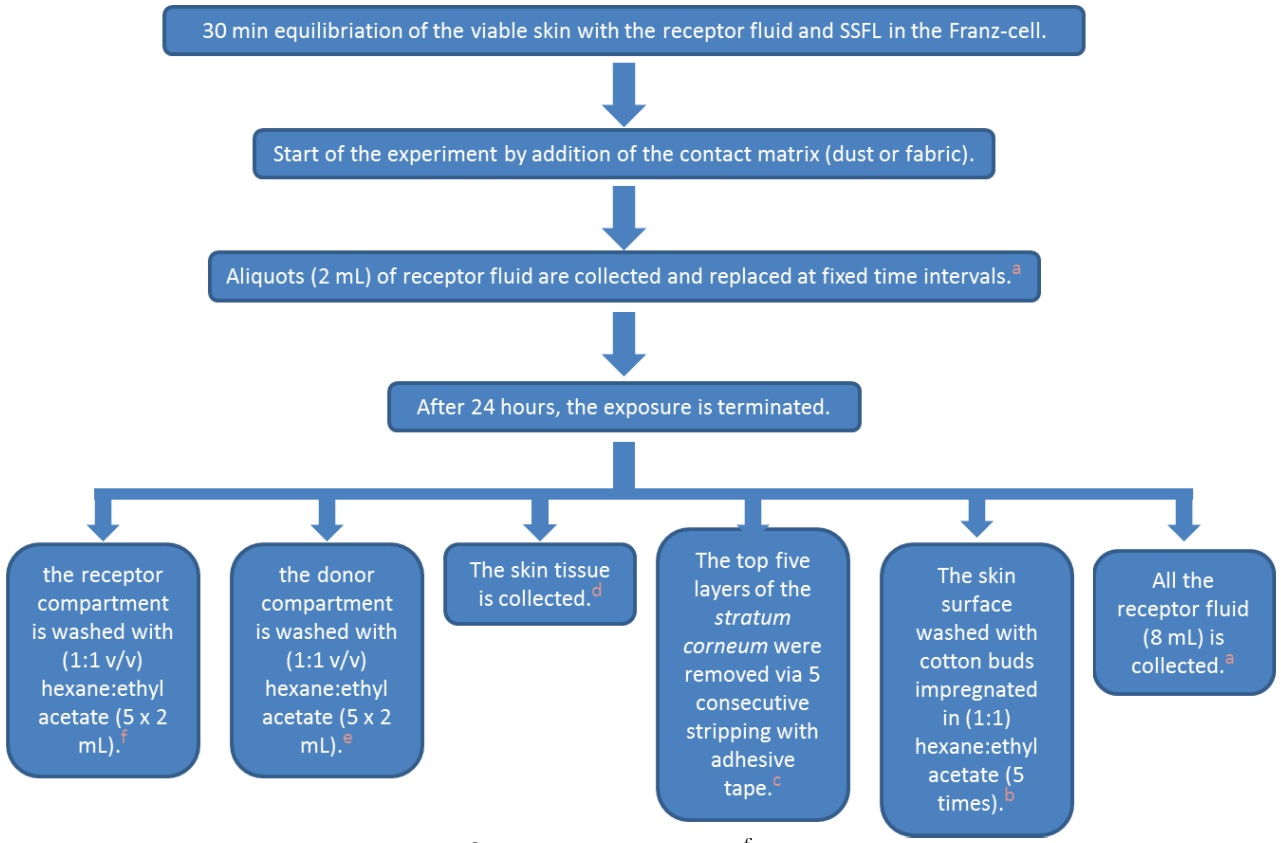


Fig.S1b.

A schematic representation of the dermal exposure protocol applied in this study.



- Concentrations of target BFRs in the receptor fluid ([a]) and receptor wash ([f]) are expressed in the mass balance as “absorbed”.
- Concentrations of target BFRs in the skin tissue ([d]) and tab strips ([c]) are expressed in the mass balance as “skin”.
- Concentrations of target BFRs in the skin wash ([b]) and donor wash ([e]) are expressed in the mass balance as “un-absorbed”.

Fig. S2

Cumulative mass (pg) of target BFRs detected in the receptor fluid following exposure of *ex vivo* human skin to 50 ng/cm^2 of indoor dust under various hydration conditions. W1 denotes skin surface wetted with 100 µL/cm^2 of SSFL, W2 denotes wetting with 50 µL/cm^2 of SSFL and D refers to non-wetted skin.

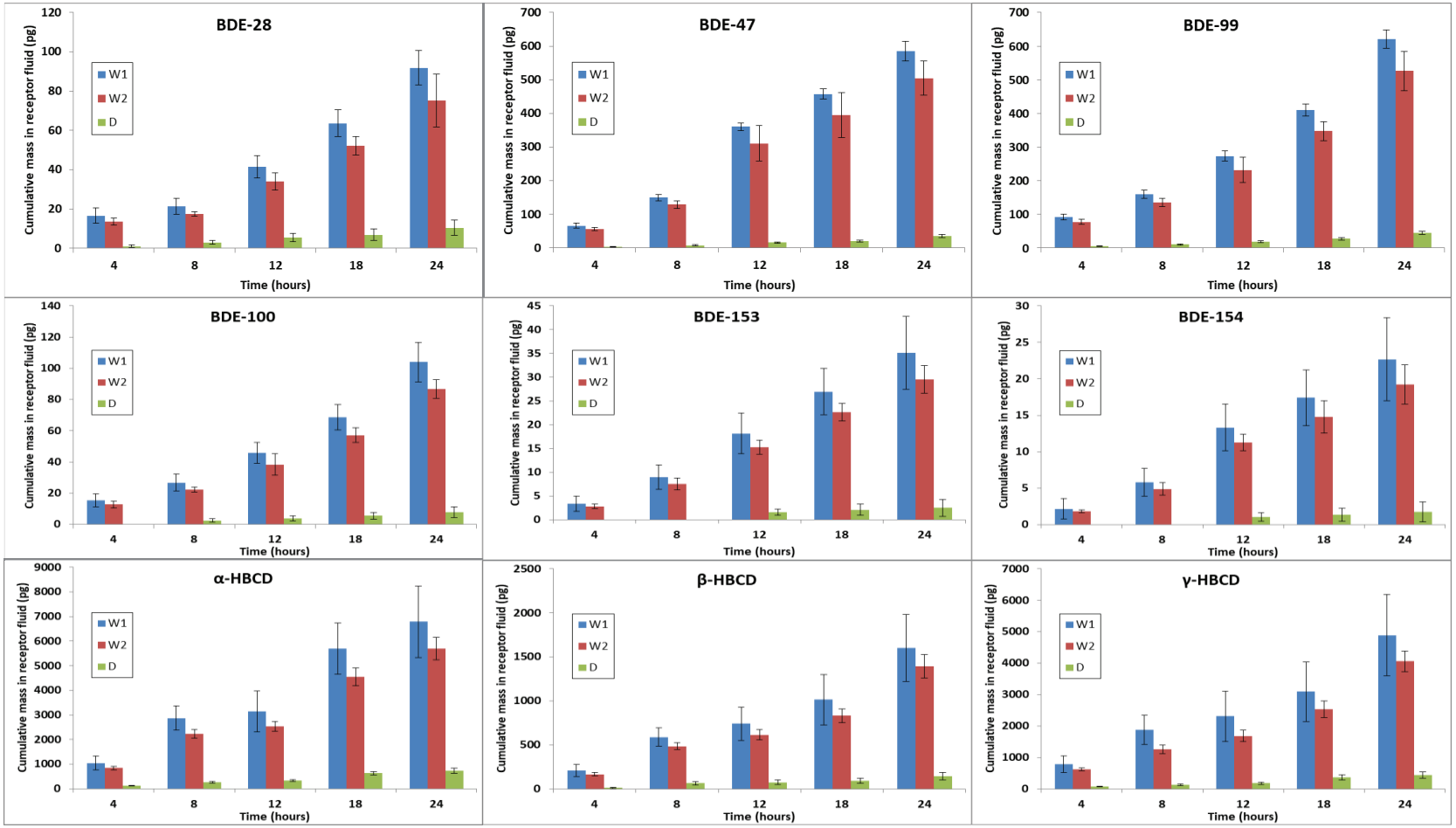


Fig. S3

Cumulative mass (ng) of target BFRs detected in the receptor fluid following exposure of *ex vivo* human skin to furniture fabrics under various hydration conditions. W1 denotes skin surface wetted with 100 µL/cm^2 of SSFL, W2 denotes wetting with 50 µL/cm^2 of SSFL and D refers to non-wetted skin.

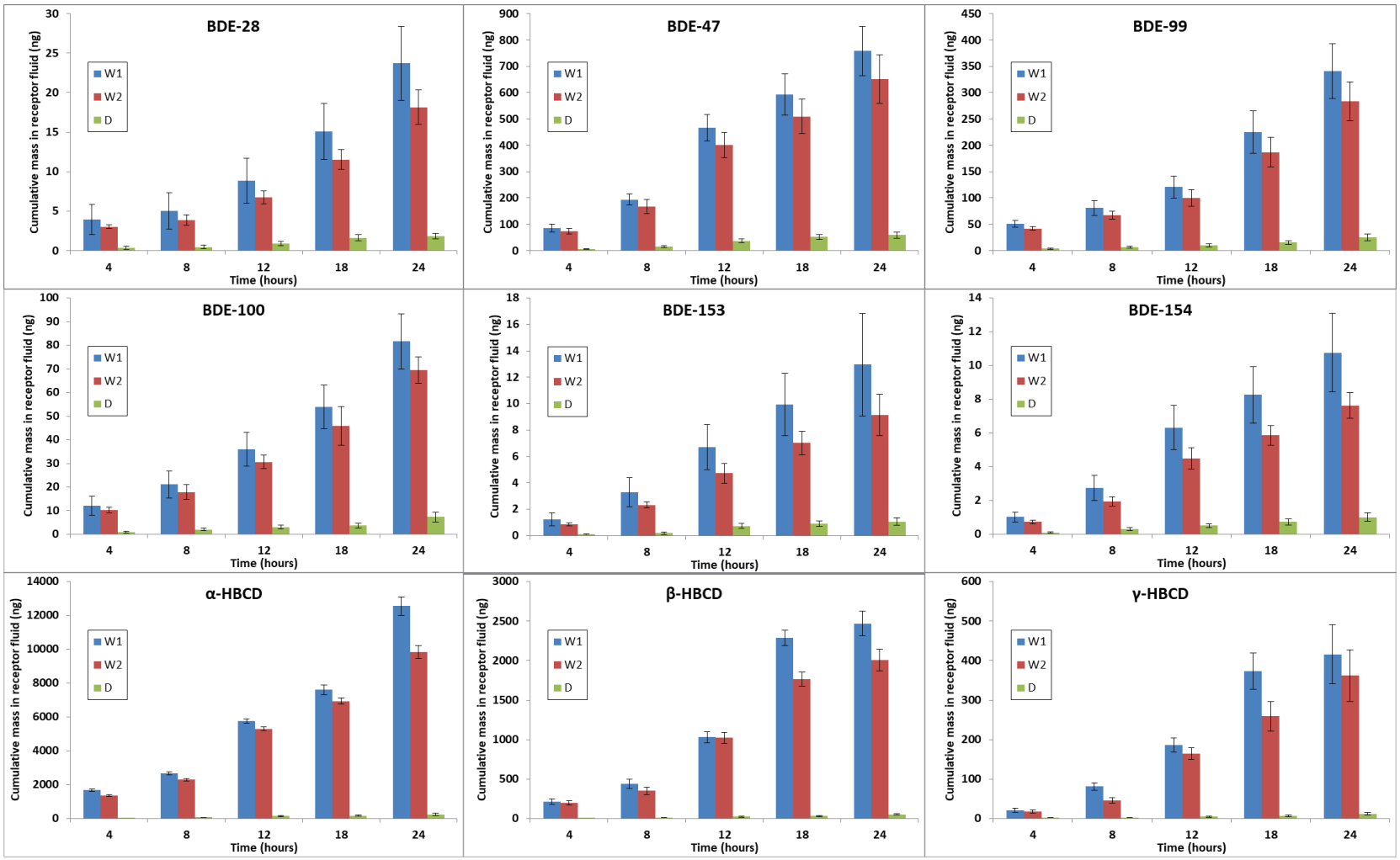


Fig. S4

Representative example of average (n=3, error bars represent 1 SD) cumulative absorbed dose (detected in the receptor fluid) of BDE-99 following dermal contact with furniture fabric (CaT9) in presence of 100 µL of SSFL.

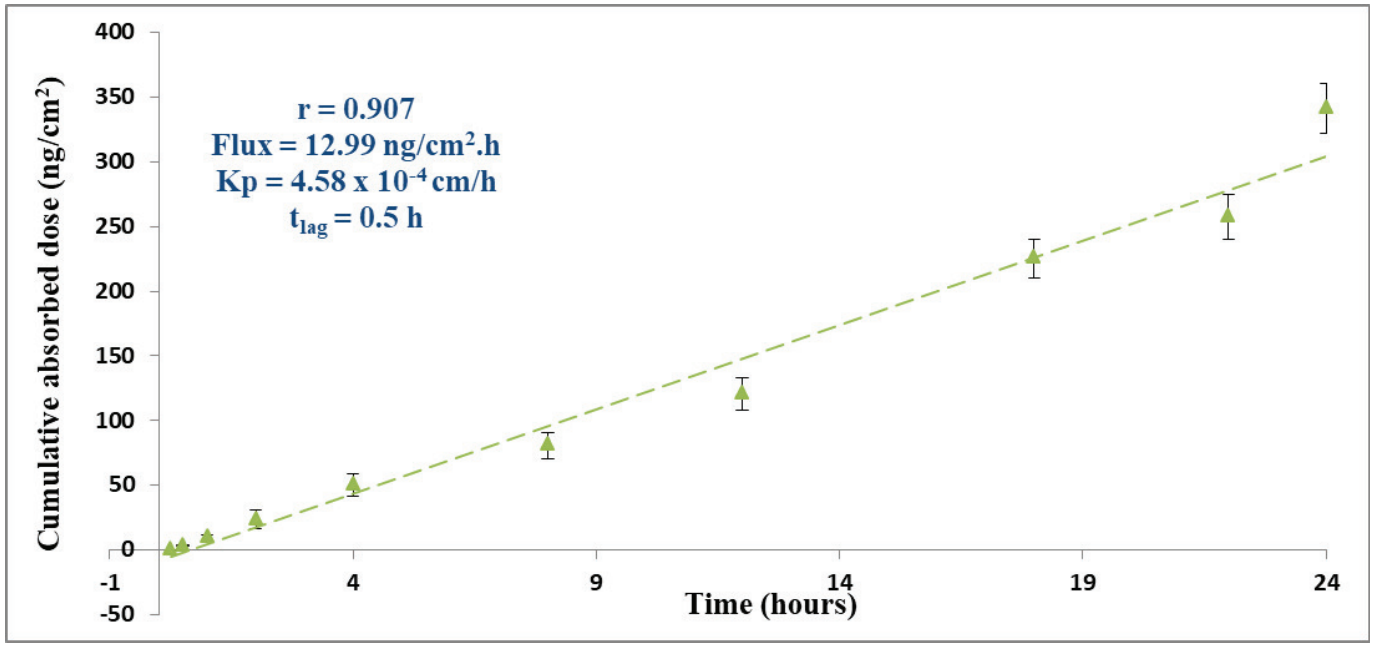


Fig. S5

Representative example of overlaid GC/MS chromatograms for BDE-47 signal. The red line shows no interference in the blank. The remaining coloured lines show detection of BDE-47 in the receptor fluid at different time points of an SRM2585 exposure experiment (until 24h), in the skin tissue (light green line) and wash (purple line) after the 24h exposure experiment.

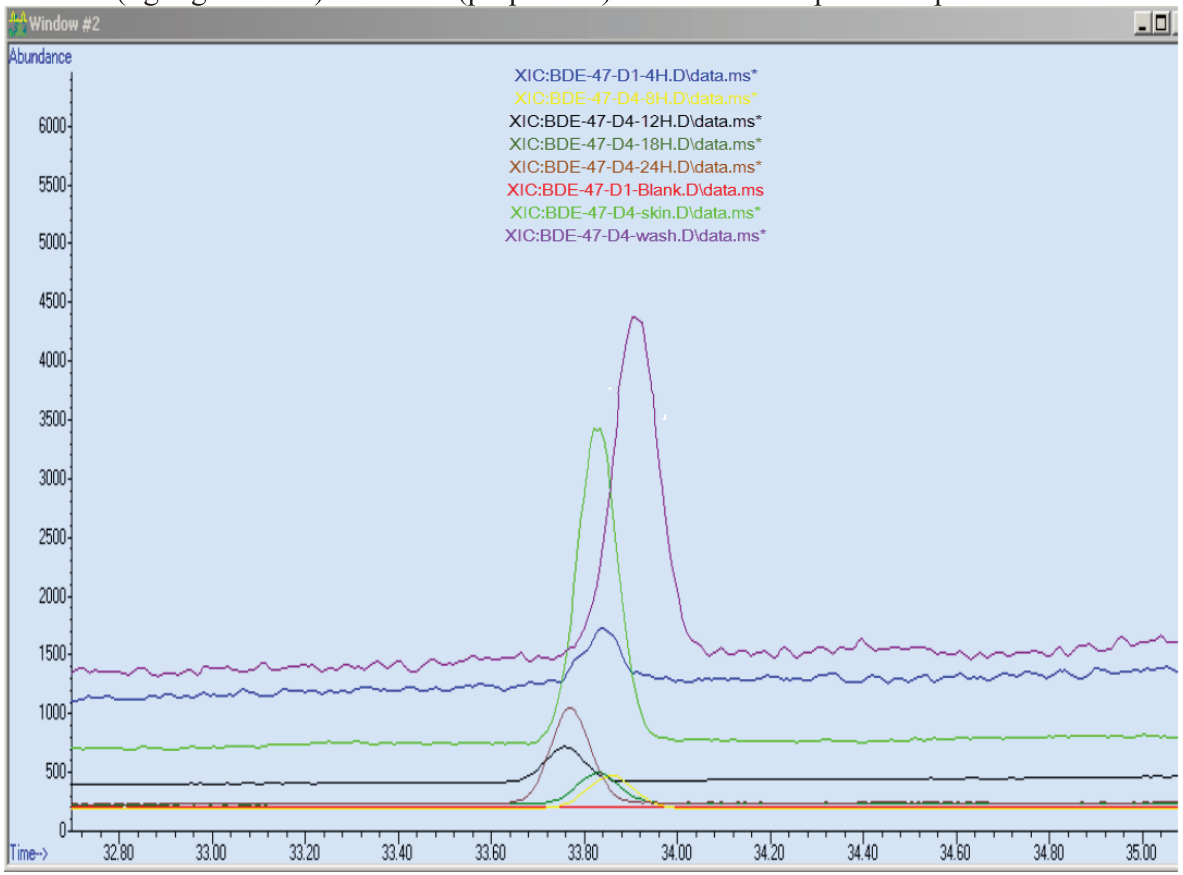


Table S1.

Components of the modified DMEM (D0422, Sigma-Aldrich, UK) medium used as maintenance/receptor fluid in this study.

Component	Concentration	Component	Concentration
Inorganic Salts	**(g/L)**	**Vitamins**	**(g/L)**
Calcium Chloride	0.2	Ascorbic Acid	0.0023
Cupric Sulfate • $5H_2O$	0.0000001	D-Biotin	0.0005
Ferric Nitrate • $9H_2O$	0.0000001	Calciferol	0.0001
Magnesium Chloride • $4H_2O$	0.0000001	Choline Cl	0.0015
Magnesium Sulfate (anhydrous)	0.0977	Folic Acid	0.001
Potassium Chloride	0.4	myo-Inositol	0.002
Sodium Bicarbonate	2.2	Menadione	0.00001
Sodium Chloride	6.8	Niacinamide	0.001
Sodium Phosphate (anhydrous)	0.122	D-Pantothenic Acid	0.001
Zinc Sulfate • $7H_2O$	0.0000002	Pyridoxal HCl	0.001
Amino Acids		Retinol acetate	0.0001
L-Alanine	0.09	Riboflavin	0.0001
L-Arginine (free base)	0.05	Thiamine • HCl	0.001
L-Asparagine • H_2O	0.02	α-Tocopherol	0.00001
L-Aspartic Acid	0.03	Vitamin B12	0.0002
L-Cysteine (free acid)	0.04	**Others**	
L-Cystine	0.02	D-Glucose	2
L-Glutamic Acid	0.0445	Glutathione	0.00005
L-Glutamine	0.0012	Methyl Linoleate	0.00003
Glycine	0.05	Phenol Red	0.0107
L-Histidine (free base)	0.015	Pyruvic Acid • Na	0.025
L-Isoleucine	0.05	Bovine serum albumin.	5 % v/v
L-Leucine	0.075	Penicillin	100 U/L
L-Lysine • HCl	0.08746	Streptomycin	100 µg/L
L-Methionine	0.015		
L-Phenylalanine	0.025		
L-Proline	0.03		
L-Serine	0.01		
L-Threonine	0.04		
L-Tryptophan	0.01		
L-Tyrosine	0.0504		
L-Valine	0.05		

Table S2.

Chemical components of simulated human skin surface film liquid (SSFL) applied in this study.

Component **Electrolytes**	Conc. (g/L)	Component **Vitamins**	Conc. (g/L)
Sodium Sulfate	5.83×10^{-2}	Thiamine HCl	1.690
Copper Chloride anhydrous	1.60×10^{-4}	Roboflavin	0.753
Ammonium Hydroxide	1.82×10^{-1}	Nicotinic Acid	50.51
Iron sulfate Heptahydrate	2.72×10^{-3}	D-Pantothenic Acid	28.50
Sulfur	7.37×10^{-2}	L-Ascorbic Acid	7.06×10^{-3}
Lead- Ref. Solution 1000 ppm	2.49×10^{-5}	Dehydroascorbic Acid	1.91×10^{-3}
Manganese- Ref. Solution 1000 ppm	1.38×10^{-4}	α-Tocopherol	5.02×10^{-3}
Nickel- Ref. Solution 1000 ppm	2.46×10^{-5}		
Zinc - Ref. Solution 1000 ppm	8.5×10^{-4}		
Sodium Bicarbonate	2.52×10^{-1}		
Potassium chloride	4.55×10^{-1}		
Magnesium Chloride Hexahydrate	1.67×10^{-2}		
Sodium Phosphate Anhydrous	4.84×10^{-2}		
Calcium Chloride Dihydrate	7.65×10^{-1}		
Sodium chloride	5.84×10^{-2}		
Organic Acids and Carbohydrates			
Acetic Acid	7.81×10^{-3}		
Butyric Acid	2.11×10^{-4}		
D(+) –Glucose	3.06×10^{-2}		
Lactic Acid	1.57×100		
Essential (17) Amino Acid Mix	2.5 mM each		
Nitrogenous Substances			
Ammonium Chloride	9.92×10^{-3}		
Urea	6.01×10^{-1}		
Creatinine	9.50×10^{-3}		
Sebum			
Squalene	0.515		
Palmityl Palmitate (wax esters, saturated)	0.972		
Oleyl Oleate (wax esters, unsaturated)	0.243		
Tristearin (triglycerides, saturated)	1.069		
Triolein (triglycerides, unsaturated)	0.535		
Cholesteryl Oleate	0.097		
Cholesterol	0.194		

Table S3.

Characterisation of indoor dust and furniture fabric samples used in this study.

Type	Code	Origin	Description	Target BFR concentrations ± SD* (ng/g)					
Dust	NIST SRM 2585	California, USA	House dust, Particle size < 150 µm	**BDE-28**	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**
				48 ± 4	514 ± 38	907 ± 41	152 ± 6	122 ± 4	80 ± 3
Dust	MD3	Birmingham, UK	House dust, Particle size < 150 µm	**α-HBCD**		**β-HBCD**		**γ-HBCD**	
				2552 ± 78		898 ± 54		3556 ± 96	
				Target BFR concentrations ± SD* (ng/cm^2)					
Fabric	CaT9	California, USA	Sofa fabric	**BDE-28**	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**
				657 ± 42	38701 ± 387	28339 ± 298	6630 ± 146	2477 ± 78	2158 ± 87
Fabric	BT5	Birmingham, UK	Armchair fabric	**α-HBCD**		**β-HBCD**		**γ-HBCD**	
				544050 ± 2600		145350 ± 1850		31050 ± 560	

*** Results are provided as average ± standard deviation of 5 measurements performed in our laboratory.**

Table S4.

Absorbed fractions, expressed as average percent of the applied dose (± standard deviation, n=3) of target BFRs measured in the receptor fluid following 24 h dermal exposure to dust* (50 mg/cm^2), fabrics* (1 cm^2) and a standard mixture of target BFRs (0.5 ng/µL/, each)$^{\$}$ in 100 µL/cm^2 of SSFL.

	Dust*	Fabric*	Neat
BDE-28	3.95 ± 0.36	3.76 ± 0.7	4.19 ± 0.32
BDE-47	2.33 ± 0.11	1.99 ± 0.06	2.98 ± 0.27
BDE-99	1.41 ± 0.09	1.21 ± 0.07	1.76 ± 0.19
BDE-100	1.44 ± 0.17	1.31 ± 0.18	1.71 ± 0.22
BDE-153	0.69 ± 0.13	0.53 ± 0.16	0.82 ± 0.27
BDE-154	0.65 ± 0.14	0.51 ± 0.11	0.76 ± 0.19
α-HBCD	5.57 ± 1.13	2.34 ± 0.12	6.07 ± 0.42
β-HBCD	3.92 ± 1.54	1.73 ± 0.10	4.41 ± 0.37
γ-HBCD	2.81 ± 0.77	1.39 ± 0.24	3.52 ± 0.44
Paired t-test$^{\#}$ for means	$P = 0.048$	$P = 0.017$	$P = 0.001$

* Full details of the dust and fabric samples used are provided in Table S3.

$^{\$}$ Final applied dose = 50 ng/cm^2 of each target BFR in the 100 µL of SSFL.

$^{\#}$ The paired t-test compares the mean absorbed fractions for all the studied BFRs between each two different matrices (i.e. dust-fabric, fabric-neat, dust-neat).

Table S5.

Absorbed fractions, expressed as average percent of the applied dose (± standard deviation, n=3) of target BFRs measured in the receptor fluid following 24 h dermal exposure to dust* (50 mg/cm^2) and fabrics* (1 cm^2) in presence of 50 and 100 µL/cm^2 of SSFL.

	Dust*		Fabrics*	
SSFL	**100 µL/cm^2**	**50 µL/cm^2**	**100 µL/cm^2**	**50 µL/cm^2**
BDE-28	3.95 ± 0.36	3.23 ± 0.56	3.76 ± 0.7	3.05 ± 0.33
BDE-47	2.33 ± 0.11	2.01 ± 0.21	1.99 ± 0.06	1.70 ± 0.15
BDE-99	1.41 ± 0.09	1.20 ± 0.13	1.21 ± 0.07	1.02 ± 0.13
BDE-100	1.44 ± 0.17	1.20 ± 0.08	1.31 ± 0.18	1.07 ± 0.08
BDE-153	0.69 ± 0.13	0.58 ± 0.05	0.53 ± 0.16	0.43 ± 0.06
BDE-154	0.65 ± 0.14	0.55 ± 0.07	0.51 ± 0.11	0.40 ± 0.04
α-HBCD	5.57 ± 1.13	4.67 ± 1.14	2.34 ± 0.12	1.82 ± 0.13
β-HBCD	3.92 ± 1.54	3.41 ± 1.39	1.73 ± 0.10	1.43 ± 0. 09
γ-HBCD	2.81 ± 0.77	2.38 ± 0.80	1.39 ± 0.24	1.25 ± 0.19
Paired t-test[#] for means	$P = 0.003$		$P = 0.003$	

* Full details of the dust and fabric samples used are provided in Table S3.

[#] The paired t-test compares the mean absorbed fractions for all the studied BFRs between the dermal application in presence of 50 µL/cm^2 and 100 µL/cm^2 SSFL to investigate the significance of skin hydration on the extent of human dermal uptake of the studied BFRs.

Table S6.

Human dermal exposure parameters applied in the current study.[4]

Exposure parameter	Adult		Toddler (4 years)	
	Male	Female	Male	Female
Surface area (cm^2)				
-Head	1360	1140	615.5	592.8
-Forearms	1460	1090	425.6	418
-back/forearms	730	545	212.8	209
-Hands	1070	870	364.8	372.4
-Palms of the hands	535	435	182.4	186.2
-Thighs	4113	3560	1140	1185.6
-back/half-thighs	1028.25	890	285	296.4
-Lower legs	2710	2300	782.8	790.4
-back/ half lower legs	677.5	575	195.7	197.6
-Feet	1380	1210	494	478.8
Body Weight (Kg)	70		15	
Exposure time (h)				
-Dust	6		9	
-Fabric	4		2	
Dust adherence to skin* (mg/cm^2)				
-Head	0.024		0.054	
-Arms	0.038		0.048	
-Hands	0.160		0.170	
-Legs	0.019		0.051	
-Feet	0.140		0.200	

* Describes the amount of solid material that adheres to the skin per unit of surface area.

Table S7.

Average recoveries (± standard deviation) expressed as percentage of the internal (surrogate) standards.

Internal standard	Average recovery (%) ± SD
BDE-77	**91 ± 10**
BDE-128	**87 ± 11**
^{13}C-BDE-209	**81 ± 17**
^{13}C-α-HBCD	**88 ± 11**
^{13}C-β-HBCD	**86 ± 8**
^{13}C-γ-HBCD	**90 ± 12**

Table S8.

Average estimated flux rates (Jss, ng/cm^2.h), permeability constants (Kp, cm/h) and lag times (t_{lag}, h) for the studied BFRs following exposure of human *ex vivo* skin to 50 ng/cm^2 of indoor dust and 1 cm^2 of furniture fabric in presence of 100 µL of SSFL.

Target BFR	Indoor dust*			Furniture fabric*		
	Flux (ng/cm^2.h)	K_p (cm/h)	t_{lag} (h)	Flux (ng/cm^2.h)	K_p (cm/h)	t_{lag} (h)
BDE-28	3.6E-03	1.49E-03	0.33	0.9	1.40E-03	0.26
BDE-47	25.2E-03	9.81E-04	0.41	32.6	8.42E-04	0.38
BDE-99	23.9E-03	5.04E-04	0.44	13.0	4.68E-04	0.51
BDE-100	4.0E-03	5.12E-04	0.42	3.1	4.74E-04	0.41
BDE-153	1.5E-03	2.46E-04	0.65	0.5	2.27E-04	0.67
BDE-154	1.1E-03	2.38E-04	0.67	0.5	2.19E-04	0.67
α-HBCD	0.30	2.32E-03	0.20	504	1.86E-03	0.25
β-HBCD	0.06	1.44E-03	0.46	114	1.15E-03	0.56
γ-HBCD	0.20	1.13E-03	0.25	19	1.02E-03	0.29

* Full details of the dust and fabric samples used are provided in Table S3.

Table S9.

Representative examples of the cumulative masses of target BFRs measured in the receptor fluid at different time points following skin exposure to HBCDs in indoor dust and fabrics for 24h in presence of 50 µl/cm^2 of SSFL.

Exp.MD3	Conc. in dust (ng/g)	Exposed skin conc. (50 mg/cm^2)	**Cumulative mass in the detector fluid (pg)**					
			Time(h)	**4**	**8**	**12**	**18**	**24**
α-HBCD	2552 ± 78	128 ng/cm^2	α-HBCD	842	2239	2539	4558	5699
β-HBCD	898 ± 54	45 ng/cm^2	β-HBCD	166	484	616	832	1393
γ-HBCD	3556 ± 96	178 ng/cm^2	γ-HBCD	624	1266	1689	2537	4059

Exp.MF3	Conc. in fabric (µg/g)	Exposed skin conc.	**Cumulative mass in the detector fluid (ng)**					
			Time(h)	**4**	**8**	**12**	**18**	**24**
α-HBCD	6045 ± 105	544050 ng/cm^2	α-HBCD	1368	2292	5301	6948	9837
β-HBCD	1615 ± 49	145350 ng/cm^2	β-HBCD	196	351	1021	1766	2008
γ-HBCD	345 ± 25	31050 ng/cm^2	γ-HBCD	18	46	164	259	362

Table S10.

Mass balance (expressed as % of exposure dose) of the studied BFRs following *in vitro* dermal exposure to indoor dust and flame-retarded fabrics.

a) Dust

Mass Balance (%)

Wet app 100 µL/cm^2	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	3.95	2.33	1.41	1.44	0.69	0.65
Un-absorbed	58.90	53.20	54.10	52.80	55.30	53.10
Skin	25.78	34.48	35.32	35.73	38.11	37.91
Sum	**88.63**	**90.01**	**90.83**	**89.97**	**94.10**	**91.66**

Mass Balance (%)

Wet app 50 µL/cm^2	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	3.23	2.01	1.20	1.20	0.58	0.55
Un-absorbed	65.19	61.07	58.45	60.72	58.36	59.62
Skin	21.08	29.74	29.94	29.78	32.03	32.14
Sum	**89.50**	**92.82**	**89.59**	**91.70**	**90.97**	**92.31**

Mass Balance (%)

Dry app	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	0.45	0.15	0.11	0.10	0.04	0.04
Un-absorbed	86.90	84.20	84.10	80.80	85.10	83.40
Skin	6.78	8.58	9.32	10.13	10.41	10.36
Sum	**94.13**	**92.93**	**93.53**	**91.03**	**95.55**	**93.80**

Mass Balance (%)

Wet app 100 µL/cm^2	α-HBCD	β-HBCD	γ-HBCD
Absorbed	5.57	3.92	2.81
Un-absorbed	64.27	66.81	68.05
Skin	18.14	18.24	19.68
Sum	**87.98**	**88.97**	**90.53**

Mass Balance (%)

Wet app 50 µL/cm^2	α-HBCD	β-HBCD	γ-HBCD
Absorbed	4.67	3.41	2.38
Un-absorbed	66.86	65.63	67.86
Skin	16.94	18.13	18.43
Sum	**88.47**	**87.17**	**88.67**

Mass Balance (%)

Dry app	α-HBCD	β-HBCD	γ-HBCD
Absorbed	0.63	0.45	0.28
Un-absorbed	85.43	86.86	85.48
Skin	2.95	2.49	2.59
Sum	**89.01**	**89.80**	**88.35**

b) Fabrics

Mass Balance (%)

Wet app 100 µL/cm^2	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	3.76	1.99	1.21	1.31	0.53	0.51
Un-absorbed	62.31	59.27	63.09	60.31	58.53	56.14
Skin	18.63	26.14	28.32	30.11	34.27	33.82
Sum	**84.70**	**87.40**	**92.62**	**91.73**	**93.33**	**90.47**

Mass Balance (%)

Wet app 50 µL/cm^2	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	3.05	1.70	1.02	1.07	0.43	0.40
Un-absorbed	80.42	83.03	82.14	83.35	82.58	82.78
Skin	5.94	6.49	7.71	7.90	9.04	9.20
Sum	**89.41**	**91.23**	**90.87**	**92.32**	**92.05**	**92.39**

Mass Balance (%)

Dry app	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154
Absorbed	0.28	0.15	0.09	0.11	0.04	0.05
Un-absorbed	86.18	88.19	85.79	87.02	88.11	86.95
Skin	1.64	2.04	2.11	2.09	3.46	3.77
Sum	**88.10**	**90.38**	**87.99**	**89.22**	**91.61**	**90.77**

Mass Balance (%)

Wet app 100 µL/cm^2	α-HBCD	β-HBCD	γ-HBCD
Absorbed	2.34	1.73	1.39
Un-absorbed	84.67	81.76	77.44
Skin	3.25	5.42	9.63
Sum	**90.27**	**88.91**	**88.46**

Mass Balance (%)

Wet app 50 µL/cm^2	α-HBCD	β-HBCD	γ-HBCD
Absorbed	1.82	1.43	1.25
Un-absorbed	85.43	84.88	82.81
Skin	2.73	4.05	7.11
Sum	**89.97**	**90.37**	**91.17**

Mass Balance (%)

Dry app	α-HBCD	β-HBCD	γ-HBCD
Absorbed	0.00	0.00	0.01
Un-absorbed	88.21	91.48	89.85
Skin	0.14	0.17	0.35
Sum	**88.36**	**91.65**	**90.21**

Table S11

Physico-chemical parameters of the studied BFRs.

Compound	Abbreviated nomenclature	Molecular Formula	Molecular Weight (amu)	Boiling Point (^{o}C, at 760 mmHg)	Water Solubility (µg/L, 25^{o}C, pH=7)	Vapour Pressure (Pa, 25 ^{o}C)	Log K_{ow}
2,4,4´- TriBDE	BDE 28	$C_{12}H_7Br_3O$	406.90	371	70	1.6×10^{-5}	5.94
2,2´,4,4´-TetraBDE	BDE 47	$C_{12}H_6Br_4O$	485.79	395	11	2.5×10^{-4}	6.81
2,2´,4,4´,5-PentaBDE	BDE 99	$C_{12}H_5Br_5O$	564.69	decomposes at > 300	2.4	5.0×10^{-5}	6.5 - 8.4
2,2´,4,4´,6-PentaBDE	BDE 100	$C_{12}H_5Br_5O$	564.69	416	40	2.1×10^{-7}	7.24
2,2´,4,4´,5,5´-HexaBDE	BDE 153	$C_{12}H_4Br_6O$	643.58	471	0.9	5.8×10^{-6}	7.90
2,2´,4,4´5,6´-HexaBDE	BDE 154	$C_{12}H_4Br_6O$	643.58	453	1	2.8×10^{-8}	7.82
α- 1,2,5,6,9,10-hexabrobocyclo dodecane	α-HBCD	$C_{12}H_{18}Br_6$	641.69	decomposes at >190	48.8	6.3×10^{-5}	5.07
β- 1,2,5,6,9,10-hexabrobocyclo dodecane	β-HBCD	$C_{12}H_{18}Br_6$	641.69	decomposes at >190	14.7		5.12
γ- 1,2,5,6,9,10-hexabrobocyclo dodecane	γ-HBCD	$C_{12}H_{18}Br_6$	641.69	decomposes at >190	2.1		5.47

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